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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/776,266	02/02/2001	Wayne Woodrow	205,011	9732

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EXAMINER
AUDET, MAURY A

ART UNIT	PAPER NUMBER
1654	

DATE MAILED: 02/26/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/776,266	WOODROW, WAYNE	
	Examiner	Art Unit	
	Maury Audet	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 November 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,10-24 and 31-37* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,10-24 and 31-37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment and Arguments

Applicant's responses of September 22, 2003 (amendment and arguments), November 11, 2003 (amendment), and November 25, 2003 (amendment) are acknowledged. Claims 3-9 have been cancelled. Claims 25-30 remain in the application, but are withdrawn as being drawn to non-elected subject matter. Claims 1-2, 10-24, and 31-37 (new) are pending and examined on the merits.

35 U.S.C.§ 112, 1st ¶, Written Description

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-2, 10-24, and 31-37 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a "written description" rejection, rather than an enablement rejection under 35 U.S.C. 112, first paragraph. Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Vas-Cath Inc. V. Mahurka, 19 USPQ2d 1111, states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in

possession of the invention. The invention, for purposes of the "written description" inquiry, is *whatever is now claimed*" (see page 1117).

The claimed invention is substantially drawn to "a stable pharmaceutical composition . . . consisting of derivatives and analogues of oxytocin and vasopressin and the salts thereof and . . . a buffer . . . free from preservatives" (claim 1); wherein the buffer is ONLY either 3 to 6 mg of citric acid/disodium phosphate dihydrate or 5 to 11 mg of citric acid/trisodium citrate dihydrate (claims 14, 34, 15, and 21; depending from claims 1 and 2 respectively).

One of skill in the art would not recognize from the disclosure that the Applicant was in possession of any buffer in any mg range, as broadly defined by claim 1. The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed" (see *Vas-Cath* at page 1116). The only two (2) buffers and ranges thereof described in the specification are "3 to 6 mg of citric acid/disodium phosphate dihydrate or 5 to 11 mg of citric acid/trisodium citrate dihydrate"; no other buffers or ranges have been described.

Thus, neither the claims nor the specification details the buffers or ranges contemplated by the genus. With the substantial variability among the broad genus (buffers and ranges thereof), it is not clear whether any buffer or any range would work in the invention. One of skill in the art would not recognize from the disclosure that the Applicant was in possession of the genus, namely all buffers and ranges.

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision (see page 1115).

Claim Rejections - 35 USC § 112 1st Scope

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-2, 10-24, and 31-37 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a range of 3 to 6 mg of citric acid/disodium phosphate dihydrate or 5 to 11 mg of citric acid/trisodium citrate dihydrate (claims 14, 34, 15, and 21; depending from claims 1 and 2 respectively), does not reasonably provide enablement for any buffer of any mg range. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The first paragraph of 35 U.S.C. 112 states, "The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same...". The courts have interpreted this to mean that the specification must enable one skilled in the art to make and use the invention without undue experimentation. The courts have further interpreted undue experimentation as requiring "ingenuity beyond that to be expected of one of ordinary skill in the art" (Fields v. Conover, 170 USPQ 276 (CCPA 1971)) or requiring an extended period of experimentation in the absence of sufficient direction or guidance (In re Colianni, 195 USPQ 150 (CCPA 1977)). Additionally, the courts have determined that "... where a statement is, on its face, contrary to generally accepted scientific principles", a rejection for failure to teach how to make and/or use is proper (In re Marzocchi, 169 USPQ 367 (CCPA 1971). Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in In re Colianni, 195 USPQ 150, 153 (CCPA 1977), have been clarified by the Board of Patent Appeals and Interferences in Ex parte Forman, 230 USPQ 546 (BPAI 1986), and are summarized in In re Wands (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed Cir. 1988). Among the factors are the nature of the invention, the state of the prior art, the predictability or lack thereof in the art, the amount of direction or guidance present, the presence or absence of working examples, the breadth of the claims, and the quantity of experimentation needed.

The instant disclosure fails to meet the enablement requirement for any buffer of any mg range in the pharmaceutical composition for the following reasons:

The nature of the invention: The claimed invention is discussed above.

The amount of direction or guidance present and the presence or absence of working examples: Enablement must be provided by the specification unless it is well known in the art. *In re Buchner* 18 USPQ 2d 1331 (Fed. Cir. 1991). The specification describes that only 3 to 6 mg of citric acid/disodium phosphate dihydrate or 5 to 11 mg of citric acid/trisodium citrate dihydrate, may be used in the invention. The specification does not even suggest that any other buffers or mg ranges are contemplated in the invention.

The breadth of the claims and the quantity of experimentation needed: The claims are drawn broadly to a pharmaceutical composition containing any buffer (and inherently any mg range). Absent sufficient teachings in the specification or art sufficient to overcome the teachings of unpredictability in the art as to enablement on whether any buffer of any range could work in the present invention to prevent adsorption of the composition/described peptides, it would require undue experimentation by one of skill in the art to be able to practice the invention commensurate in scope with the claims.

Claim Rejections - 35 USC § 112 2nd

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-2, and thus claims 10-24, and 31-37 are rejected under 35 U.S.C. 112, second paragraph, as failing to set forth the subject matter which applicant(s) regard as their invention.

Evidence that these claims fail(s) to correspond in scope with that which applicant(s) regard as the invention can be found in specification, which Example 5, which states the "quality attributes required for the compositions of the present invention are . . . PH 3.5-6.0". Applicant invention is stated to prevent adsorption without the use of preservatives. No clear indication was found in the specification on how this is possible. Therefore, the only "quality" that appears to be associated with this adsorption prevention is the maintenance of a "PH 3.5-6.0". Although this limitation has been claimed in later dependent claims 13 and 36, it has not been claimed in broad claims 1 or 2, the independent claims which set forth the invention. Therefore, the PH (3.5-6.0) "quality attribute" is deemed essential to the invention, absent evidence to the contrary, and is required to be set forth so as to claim the subject matter which applicant(s) regard as their invention.

Claims 1-2, 10-24, and 31-37 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claims 1 and 2 it is unclear what is contemplated by "stable"? Stable is a relative term, which could mean a few minutes to years, depending on the use of the composition in question or the artisan's definition of stable. "Stable" is not a well known scientific principle, which has been defined by art as equating to specific parameters of time or otherwise. The specification page 1 refers to a composition "stable before and during use". The examples teach that the composition was tested for adsorption percentages at 4 days and 18 months. However, nowhere is it defined what "stable" means as contemplated by the invention. The invention appears to

focus on "adsorption" over a period of time, but never defines "stable" as referring to "adsorption levels". It is suggested that the claims be amended to be drawn to "adsorption" limitations over time (namely 4 days to 18 months), to which "stable" may still be used in the claim language, assuming clear support can be shown for the use of "stable" with such a timeframe limitation.

In claim 1 it is unclear what is contemplated by "it" (line 5)? Namely, whether "it" refers to the peptide or the composition. Appropriate amendment is required.

In claim 1, it is unclear what is contemplated by "adsorption inhibitors preventing adsorption of the active principle onto container walls and free from antioxidants and antimicrobial additives"? Applicant has removed the limitation to "preservatives", and the added phrase above is therefore unclear, since the specification defines that the invention's preservative IS defined on page 3 as "degradation inhibitors (antioxidants and antimicrobial additives) as well as adsorption inhibitors (preventing adsorption of the active principle onto container walls)". It is suggested that "preservatives" be put added back into the claim followed by the quoted material above.

In claim 1 the language "inhibitors preventing adsorption" is confusing. Although the same phrase was used in the specification (page 3), it is suggested that the phrase be amended to "inhibitors which prevent" to clarify the claim limitation.

Claim 1 recites the limitation "the active principle". There is insufficient antecedent basis for this limitation in the claim. It is unclear what is contemplated by "the active principle" in the claim as well as the specification (page 3), namely whether applicant is referring to the

peptide or the composition. Clarification and where needed, amendment (with support), is required.

Claim 2 recites the limitation "consisting of". There is insufficient antecedent basis for this limitation in the claim. Claim 2 is limited to a composition with only "derivatives and analogues of oxytocin and vasopressin and the salts thereof and . . . a buffer ". However, the invention is drawn to essentially known peptides in a composition, that is "free from preservatives". Although closed language "consisting of" has been used, the invention has not been distinctly claimed, namely that the composition must be "free from preservatives". Clarification is required.

Claim Rejections - 35 USC § 103

The original rejection of claims 1-24 under 35 U.S.C. 103(a) as being unpatentable over Bengtsson (5763398) in view of Harris et al. and Fredholt et. Al. (Int. J. Pharm. 1999) and Florin-Robertsson et al. (US 5783559) is maintained. Applicant's arguments filed September 22, 2003 have been fully considered but they are not persuasive. Applicant has argued that Bengtsson "fails to disclose -even accidentally- a stable pharmaceutical composition free from adsorption inhibitors and free from antioxidants and antimicrobial additives" or any "behavior over time". To the contrary, *it is well known scientifically that buffers can maintain a pH of 4 to 6, and that maintaining such a pH provides stability to a composition.* The aforementioned leads to the conclusion that Applicant's argument that Bengtsson does not discuss any "behavior over time" is also nonpersuasive, since Bengtsson reference teach the optional addition of buffers to maintain a pH of 4 to 6, that would intrinsically provide stability to the Bengtsson composition.

[Note: Likewise, there is no inference from Bengtsson that preservatives have to be in the composition, only that they *may*; or that any of the listed additives *all* have to be added, only that any of the list *may* be (emphasis added)]. Additionally, Applicant has argued that since Bengtsson does not teach the use of buffers to maintain pH as "critical" to the invention, that Bengtsson must have put it in there for it's "legalistic language and not from a scientific investigation of *stability*". This argument is also deemed wholly unpersuasive, since a) Applicant has no idea whether Bengtsson additionally included the use of buffers to maintain a pH of 4 to 6 for legalistic reasons, and b) even for sake of argument, if this were the case, Bengtsson teach it as an option and *buffers are nevertheless well known scientifically to maintain a pH of 4 to 6, the latter of which is also well known scientifically to provide stability to a composition* [like Applicant's buffer/ph combination for stability]. Therefore, whether Bengtsson did or did not attempt to reinvestigate the known scientific principle that buffers provide *stability* to compositions by maintaining pH balance, is entirely irrelevant. Bengtsson teaches that "buffers designed to maintain a pH of 4 to 6" *may* be used, and it is well known in the art that maintaining pH provides stability to a composition. *Therefore, it is clear that one of skill in the art who chose to use Bengtsson's listed buffers or related buffers to maintain a pH of 4 to 6, would intrinsically provide such a composition with stability, like that of Applicant's.*

The rejection is now reapplied below to the amended and new claims.

Claims 1-13, 15-18, 31-33, and 36-37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bengtsson (5763398) in view of Fredholt et. Al. (Int. J. Pharm. 1999), and further in view of Harris et al. and Florin-Robertsson et al. (US 5783559).

As discussed in the previous action, Bengtsson teach desmopressin acetate, 0.1 to 2.0 mg/ml, in an aqueous pharmaceutical composition (claim 1; "about 75 ul"=.75ml), which may include a buffer selected from sodium phosphates or sodium citrates to maintain a pH between 4 and 6, and sodium chloride as the osmotic-pressure controlling agent (column 3, lines 33-11). [Note: Bengtsson teach that preservatives *may* be included, among other additives, but do not have to (column 3, lines 4-6); and as claimed the composition does not include a preservative (claim 1)][Applicant's claims 1-2, 10, 12-13, and 15-18].

Bengtsson teach that any salts (i.e. analogs) of desmopressin may be used in the present invention (column 3, line 17). However, Bengtsson does not expressly teach use of a mercaptopropanol derivative. [Applicant's claim 11 and 32].

Fredholt et al. teach the use of [1-(mercaptopropanoic acid)-8-D-arginine vasopressin; dDAVP], which has a "selective antidiuretic effect" in water, without preservatives (abstract).

It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to use the desmopressin analog of Fredholt et al. as one of the analogs of desmopressin contemplated for use in Bengtsson, because Fredholt et al. teach that [1-(mercaptopropanoic acid)-8-D-arginine vasopressin; dDAVP] has a selective antidiuretic affect, wherein greater receptor selectivity is a desired affect of pharmaceutical compositions and

because Bengtsson teach that other related desmopressin salts are contemplated for use in the invention (col. 1, lines 37-40).

Claims 1-2, 10-24, and 31-37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bengtsson (5763398) in view of Fredholt et. al. (Int. J. Pharm. 1999), and further in view of Harris et al. and Florin-Robertsson et al. (US 5783559).

Bengtsson and Fredholt et al. are discussed above. Bengtsson et al. teach a buffer selected from sodium phosphates or sodium citrates to maintain a pH between 4 and 6 (column 3, lines 33-11). Bengtsson et al. does not specifically teach citric acid/disodium phosphate dihydrate/trisodium citrate dihydrate combinations. [Applicant's claims 14, 19-24, and 34-45].

Harris et al. teach the use of disodium phosphate dihydrate and citric acid monohydrate (col. 3, lines 17-24).

Florin-Robertsson et al. teach trisodium buffer 10.5 mg, teach the use of citrate buffers for protein stability (i.e. IGF, a small peptide, with 3 disulfide bonds) (col. 5, Ex. 5), and specifically trisodium citrate dihydrate 10.5 mg. Florin-Robertsson et al. also teach the use of trisodium citrate dihydrate and disodium phosphate dihydrate.

It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to use the buffer combinations and mg levels of either Harris et al. and Florin-Robertsson et al. in combination with the citrate and phosphate buffers of Bengtsson, because Harris et al. and Florin-Robertsson et al. teach that their respective buffers may be used to effectively maintain the desired pH of a composition containing a peptide; and routine optimization with known buffers would be within the skill of one in the art.

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maury Audet whose telephone number is 703-305-5039. The examiner can normally be reached from 7:00 AM – 5:30 PM, off Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached at 703-306-3220. The fax phone numbers for the

organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-308-1234 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235.

MA
February 7, 2004

CHRISTOPHER R. TATE
PRIMARY EXAMINER